ASSOCIATION BETWEEN EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE AND EXACERBATIONS OF ASTHMA IN CHILDREN

BARBARA A. CHILMONCZYK, M.D., LUIS M. SALMUN, M.D., KEITH N. MEGATHLIN, M.D., LOUIS M. NEVEUX, B.S., GLENN E. PALOMAKI, B.S., GEORGE J. KNIGHT, PH.D., ANDREA J. PULKKINEN, M.S., AND JAMES E. HADDOW, M.D.

Abstract *Background.* Exposure to environmental tobacco smoke, as reported by parents, has been linked to diminished pulmonary function and more frequent exacerbations of asthma in children with the disease. Further insight into this association might be gained by using urine cotinine levels to measure actual exposure.

Methods. We measured urine cotinine levels in 199 children with asthma; 145 also underwent pulmonary-function studies. A parent answered questions about each child's exposure to environmental tobacco smoke. Acute exacerbations of asthma during the preceding year were documented through blinded review of medical records. Possible confounding factors were accounted for by the use of multivariate analysis and by comparisons of serum theophylline levels in exposed and unexposed children.

Results. The median urine cotinine levels were 5.6 ng per milliliter in the 116 children reported not to have been exposed to tobacco smoke, 13.1 ng per milliliter in the 53 children exposed to cigarette smoking by the mother or other persons, and 55.8 ng per milliliter in the 30 children exposed to cigarette smoking by the mother and other persons. Acute exacerbations of asthma increased with exposure, whether such exposure was reported by a parent or identified on the basis of the cotinine level; the relative risks for the highest as compared with the lowest exposure category were 1.8 (95 percent confidence interval, 1.4 to 2.2) for reported exposure and 1.7 (95 percent confidence interval, 1.4 to 2.1) for exposure indicated by cotinine levels. The forced expiratory volume in one second (FEV_1), the forced expiratory flow between 25 and 75 percent of vital capacity, and the ratio of FEV, to forced vital capacity also decreased with increases in both measures of exposure.

Conclusions. Measurement of urine cotinine levels provides further evidence of an association between exposure to environmental tobacco smoke and pulmonary morbidity in children with asthma. These data emphasize the need for systematic, persistent efforts to stop the exposure of children with asthma to environmental tobacco smoke. (N Engl J Med 1993;328:1665-9.)

ASTHMA is the most common chronic lung disorder in children; it affects approximately 2 million to 5 million children in the United States. Exposure to environmental tobacco smoke has been reported to affect children with asthma adversely in a variety of ways; its effects include a decrease in pulmonary function,[1-3] an increase in airway reactivity,[1-6] and an increase in the frequency of visits to the emergency room for treatment of acute exacerbations of asthma.[7] Three studies have suggested that children exposed to environmental tobacco smoke may have a higher-than-average risk of asthma.[8-10]

To date, the published studies that have examined the consequences of exposure to environmental tobacco smoke in children with asthma have relied exclusively on parents' reports of their smoking habits. Even reliable parental reports of exposure to environmental tobacco smoke could be relatively inaccurate, however, as a measure of children's actual inhalation of such smoke. Although this inaccuracy is not likely to interfere with analyses comparing exposed and unexposed groups, it could make it difficult to detect a dose–response relation. If cotinine measurements were found to be consistent with parental reports of children's exposure to environmental tobacco smoke, this measurement could provide additional validation for published studies that have linked reported exposure to pulmonary morbidity. Moreover, if a dose–response relation were identified between morbidity and cotinine levels, this relation would strengthen the argument in favor of causality and lessen the possibility that exposure to environmental tobacco smoke serves only as a marker for other environmental or socioeconomic factors.

We used urine cotinine levels in addition to parental reports to examine these questions further in a population of children who were receiving ongoing specialized care for asthma. Cotinine, a metabolic derivative of nicotine, is excreted in the urine and serves as an accurate, short-term quantitative measure of the intake of tobacco smoke. The circulating half-life of cotinine is approximately 24 hours.[11,12] In this study, pulmonary-function measurements and acute exacerbations of asthma were the health-related end points analyzed in relation to both parental reports of exposure to environmental tobacco smoke and urine cotinine concentrations.

METHODS

Study Population

From February 20 through May 9, 1992, 204 children with asthma (age, 8 months to 13 years) and the parents who accompanied them to routine visits at a large allergy–asthma practice in Portland, Maine, were asked by the office staff whether they were willing to take part in a clinical study. The study had been approved by the institutional review boards of the Foundation for Blood Research and the Maine Medical Center. A total of 199 pairs of children and parents agreed to participate, and the parents gave written consent. At enrollment, each parent filled out a questionnaire, and a urine sample was obtained from each child. In addition to obtaining demographic data about the child, the questionnaire sought information on the following: the parents' occupations and years of education completed; the number of people in the household; the age at which the child was given a diagnosis of asthma; the child's current

From the Foundation for Blood Research, Scarborough, Me. (B.A.C., L.M.N., G.E.P., G.J.K., A.J.P., J.E.H.); and the Maine Medical Center, Portland (B.A.C., L.M.S., K.N.M.). Address reprint requests to Dr. Haddow at the Foundation for Blood Research, P.O. Box 190, Scarborough, ME 04070-0190.

Supported by a grant from the Maine Medical Center Research Department and by internal funding from the Foundation for Blood Research.

medication status; the child's school status; use of day care outside of the home; smoking at the day-care site, including an estimate of the amount; the current smoking status of the accompanying parent, including the number of cigarettes smoked per day and the estimated number of hours per week of smoking in the home; and the current smoking status of all others in the household, including the estimated number of cigarettes (or cigars or pipes) smoked per day.

Pulmonary-function tests were also performed at enrollment in the 145 children who were capable of performing the forced expiratory maneuver. All the children's medical records were reviewed in a blinded fashion to determine the number of acute exacerbations of asthma during the 12 months before enrollment and to obtain information about use of medications. Using published guidelines from the National Heart, Lung, and Blood Institute,[13] we classified asthma as mild in 47 of the children (23.6 percent), moderately severe in 145 (72.9 percent), and severe in 7 (3.5 percent).

Urine Cotinine and Creatinine Analyses

Urine samples were frozen and stored to be analyzed in batches. The measurement of cotinine was performed with use of an iodine-125 competitive radioimmunoassay, the details of which have been previously reported.[14] Creatinine was also measured in each sample, with use of a commercially available kit (Sigma Diagnostics, St. Louis).

Statistical Analysis

In an earlier study,[15] urine cotinine levels were found to be consistent with exposure to environmental tobacco smoke at a level of 10 ng per milliliter (57 nmol per liter) or higher. Continuous variables were compared by t-test after appropriate transformations of the data. Categorical variables were compared with the chi-square test. Cotinine levels were corrected for the concentration of the urine by fitting the relation between the log cotinine level and the log creatinine level,[16] with use of a second-order curve. The dose–response relation between the two measures of exposure to environmental tobacco smoke and the results of the four pulmonary-function tests was assumed to be linear. Stepwise multivariate linear-regression analysis was, therefore, used to estimate the extent of the change in pulmonary function associated with increasing levels of exposure. In this analysis we controlled for the mother's age and education level and the child's age, sex, and attendance at day care. To allow a direct comparison between reported exposure and cotinine levels, the cotinine cutoff points were chosen to include the same number of children in each category of cotinine intake as dictated by the reported exposure categories. All analyses were performed with the BMDP statistical package.[17]

Results

Table 1 compares selected characteristics of the study population according to the presence or absence of reported exposure to environmental tobacco smoke. According to parental reports, 83 (42 percent) of the children were exposed to environmental tobacco smoke. Boys predominated in both the nonexposed and the exposed categories. In households where exposure to environmental tobacco smoke was reported, the average age of the mothers was younger, they had fewer years of education, and children's enrollment in day care was more frequent. Urine cotinine measurements were significantly higher when exposure to environmental tobacco smoke was reported.

Figure 1 shows urine cotinine concentrations in relation to exposure to environmental tobacco smoke as reported by the parents. The median cotinine concentrations increased monotonically in the three defined categories (no exposure to environmental tobacco smoke, exposure to smoking by the mother or other persons, and exposure to smoking by the mother and other persons). Of the 116 cotinine measurements in the group with no reported exposure to environmental tobacco smoke, 100 were below 10 ng per milliliter, a level previously established as consistent with minimal exposure; except for 1 cotinine measurement of 40 ng per milliliter (228 nmol per liter), the highest level in this group was 20 ng per milliliter (114 nmol per liter). Of the 30 cotinine measurements in the group with the highest reported level of exposure (smoking by the mother and other persons), all were above 10 ng per milliliter, and all but 3 were above 20 ng per

Table 1. Characteristics of Children with Asthma, According to Parental Reports of Exposure to Environmental Tobacco Smoke.*

Characteristic	No Exposure	Exposure	P Value
No. of children	116	83	—
Percent boys	75	67	0.3
Percent in school	82.6	80.7	0.7
Percent in day care	18.1	49.4	<0.001
Age at enrollment (yr)	7.4±2.8	7.6±2.9	0.7
Age at diagnosis (yr)	4.0±2.8	4.3±2.6	0.6
Mother's age at enrollment (yr)	35.4±4.5	33.1±6.3	0.01
Mother's education (yr)	15.0±2.4	13.0±1.8	<0.001
No. of people in household	4.2±0.9	4.1±1.1	0.6
Urine cotinine level (ng/ml)	5.6±0.33†	23.3±0.44†	<0.001

*Plus–minus values are means ±SD, unless otherwise noted.

†The median ±SD of the $\log_{10}$ cotinine level. To convert values for cotinine to nanomoles per liter, multiply by 5.7.

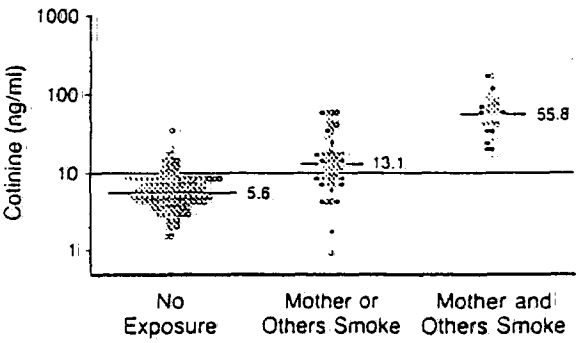

Figure 1. Relation between Reported Exposure to Environmental Tobacco Smoke and Urine Cotinine Concentrations in 199 Children with Asthma.

Urine cotinine concentrations (corrected for the creatinine concentration) are represented on a logarithmic scale. Three mutually exclusive levels of exposure to environmental tobacco smoke reported by parents are shown. Solid circles identify children in day-care settings in which exposure to environmental tobacco smoke was reported. The horizontal line at 10 ng of cotinine per milliliter is an arbitrary demarcation point, above which exposure to environmental tobacco smoke was considered substantial. Median cotinine levels are indicated for the three exposure levels. To convert values for cotinine to nanomoles per liter, multiply by 5.7.

milliliter. Cotinine measurements in the intermediate-exposure group (smoking by the mother or other persons) were less consistent, indicating more variable intake of tobacco smoke. Reported exposure to environmental tobacco smoke in the day-care setting did not add measurably to the children's cotinine levels, over and above household exposure. Table 2 shows the extent to which parental reports of exposure to environmental tobacco smoke correlated with measurements of cotinine in urine. Overall, when the cutoff level of 10 ng per milliliter was used for urine cotinine, the two methods agreed for 164 of the 199 children.

Table 2. Agreement between Urine Cotinine Levels and Reported Exposure to Environmental Tobacco Smoke in Children with Asthma.*

Cotinine Level	Exposure	No Exposure	Total
≥10 ng/ml	64	16	80
<10 ng/ml	19	100	119
Total	83	116	199

*To convert values for cotinine to nanomoles per liter, multiply by 5.7.

Table 3 demonstrates that, as reported exposure to environmental tobacco smoke increases, acute exacerbations of asthma increase and pulmonary function decreases. A monotonic pattern of increased morbidity was found for acute exacerbations of asthma but not for the measures of pulmonary function. The observed changes in the four measures of morbidity due to asthma for each increase in the category of exposure to environmental tobacco smoke were initially analyzed with use of simple linear regression analysis (observed) and then further analyzed with use of a multivariate linear regression model that included the mother's age and education level and the child's age, sex, and day-care attendance (adjusted). The 95 percent confidence intervals for the adjusted estimates indicate that three of the four measures of morbidity were significantly worse with increasing exposure to environmental tobacco smoke. For the number of acute exacerbations in the previous year, the adjusted relative risk for the highest as compared with the lowest exposure category was 1.8 (95 percent confidence interval, 1.4 to 2.2).

Table 4 repeats the analyses in Table 3, but in this case we used urine cotinine measurements, rather than parental reports, to measure the intake of environmental tobacco smoke. The same trends were found as in Table 3, but a monotonic pattern was found for both the increase in acute exacerbations of asthma and the decrease in the measures of pulmonary function. After adjustment for potential confounders, the 95 percent confidence intervals for three of the four measures indicated that significantly increased morbidity due to asthma was associated with the actual intake of environmental tobacco smoke. The relative risk for the number of acute exacerbations of asthma in the previous year in the highest as compared with the lowest intake category was 1.7 (95 percent confidence interval, 1.4 to 2.1), after adjustment for possible confounders.

The extent to which the information provided by reported exposure to environmental tobacco smoke overlaps with that provided by cotinine measurements can be examined by testing the effect of adding one of these measures (cotinine levels or reported exposure) to a multivariate model that already contains the other, along with possible confounders. When reported exposure was tested in relation to acute exacerbations of asthma in this multivariate model, it added significant predictive power ($F = 5.99$, $P = 0.02$), whereas cotinine levels did not ($F = 0.05$, $P = 0.8$). In relation to pulmonary function, neither cotinine levels nor reported exposure added significant predictive power to a model already containing the other (for reported exposure: $F = 0.35$, $P = 0.6$ for the relation to the forced expiratory volume in one second [FEV_1]; $F = 0.48$, $P = 0.5$ for the relation to the forced expiratory flow between 25 and 75 percent of vital capacity [FEF_{25-75}]; and $F = 1.01$, $P = 0.3$ for the relation to the ratio of FEV_1 to forced vital capacity [FVC]; for cotinine measurements: $F = 2.82$, $P = 0.1$ for the relation to FEV_1; $F = 1.73$, $P = 0.2$ for the relation to FEF_{25-75}; and $F = 2.01$, $P = 0.2$ for the relation to FEV_1:FVC).

Theophylline was prescribed for 104 of the 199 children with asthma during the year before enrollment, including 45 (54 percent) of the 83 exposed to environmental tobacco smoke and 59 (51 percent) of the 116 not exposed. Serum theophylline levels were available for 27 of the exposed children and

Table 3. Current Pulmonary Function and Number of Acute Exacerbations of Asthma during the 12 Months before Enrollment, According to Reported Exposure to Environmental Tobacco Smoke.*

Variable	No Exposure	Mother or Others Smoke	Mother and Others Smoke	Change per Category of Increasing Exposure	
				Observed	Adjusted (95% CI)†
No. of children‡	166/83	53/41	30/21	—	—
No. of acute exacerbations	2.2±2.0	2.5±1.6	3.9±2.7	0.75	0.83 (0.39 to 1.26)
FEV_1 (%)	109.3±20.7	102.4±26.0	102.2±17.9	−4.3	−2.3 (−7.9 to 3.3)
FEF_{25-75} (%)	85.4±26.7	71.8±30.6	73.6±19.3	−7.6	−8.2 (−15.4 to −1.0)
Ratio of FEV_1 to FVC (×100)	83.7±7.6	79.4±8.4	80.0±7.0	−2.4	−3.1 (−5.0 to −1.0)

*Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in one second; FEF_{25-75} forced expiratory flow between 25 and 75 percent of vital capacity, and FVC forced vital capacity.

†Adjusted for the mother's age and education level and the child's age, sex, and day-care attendance. CI denotes confidence interval.

‡The number available for the analysis of acute episodes of asthma, followed by the number available for the analysis of pulmonary-function studies.

Table 4. Current Pulmonary Function and Number of Acute Exacerbations of Asthma during the 12 Months before Enrollment, According to Intake of Environmental Tobacco Smoke as Defined by the Urine Cotinine Level.*

VARIABLE	COTININE			CHANGE PER CATEGORY OF INCREASING INTAKE	
	<10 ng/ml	10–39 ng/ml	>39 ng/ml	OBSERVED	ADJUSTED (95% CI)†
No. of children‡	116/83	53/41	30/21	—	—
No. of acute exacerbations	2.1±1.9	2.8±1.8	3.6±2.9	0.80	0.63 (0.10 to 1.07)
FEV_1 (%)	108.8±20.3	105.2±24.7	98.5±22.3	−4.8	−4.7 (−9.9 to 0.5)
FEF_{25-75} (%)	85.4±26.8	74.9±28.8	67.3±22.8	−9.4	−8.5 (−15.2 to −1.9)
Ratio of FEV_1 to FVC (×100)	83.5±7.5	81.2±8.1	77.5±8.0	−2.8	−3.0 (−4.9 to −1.1)

*Plus–minus values are means ±SD. FEV_1 denotes forced expiratory volume in one second; FEF_{25-75} forced expiratory flow between 25 and 75 percent of vital capacity, and FVC forced vital capacity. Urine cotinine concentrations have been adjusted for the creatinine concentration. To convert values for cotinine to nanomoles per liter, multiply by 5.7.

†Adjusted for the mother's age and education level and the child's age, sex, and day-care attendance. CI denotes confidence interval.

‡The number available for the analysis of acute episodes of asthma, followed by the number available for the analysis of pulmonary-function studies.

36 of the unexposed children. When more than one measurement was available for a given child during the preceding year, only the first was included in the analysis. Measurable theophylline levels were present in all 63 of the children. The mean serum theophylline levels of 11.37 μg per milliliter (62.5 μmol per liter) in the exposed children and 11.42 μg per milliliter (62.8 μmol per liter) in the unexposed children were similar ($t = -0.04$, $P = 0.97$).

Discussion

Data from this study provide further validation of published reports that exposure to environmental tobacco smoke adversely affects the health of children with asthma.[1-9,18] Furthermore, the cotinine measurements in this study group provide information not previously available: parental reports indicating no exposure to environmental tobacco smoke were consistent with cotinine measurements 86 percent of the time, and parental reports indicating exposure were consistent with measured levels 77 percent of the time. Discrepancies between parental reports and cotinine measurements might be explained by incomplete knowledge of exposure, on the one hand, or variability in environmental conditions leading to diminished inhalation of environmental tobacco smoke, on the other. Purposeful misreporting of smoking habits is unusual.[11,12] Cotinine is a measure of actual recent intake of smoke from cigarette products and, as such, will not always agree with the reported smoking habits of nearby persons.

Significant increases in the frequency of acute exacerbations of asthma were found whether exposure to environmental tobacco smoke was identified on the basis of parental reports or urine cotinine levels, and monotonic dose–response patterns were evident with both methods. Significant reductions in pulmonary function were also found, whether exposure to environmental tobacco smoke was assessed on the basis of parental report or cotinine level, and linear dose–response patterns were evident when the exposure was defined by the cotinine level. The linear dose–response patterns provide further evidence of a causal relation between exposure to environmental tobacco smoke and pulmonary morbidity in children with asthma.

Some or all of the morbidity associated with exposure to environmental tobacco smoke may be attributable to the differences between the exposed and unexposed populations (Table 1). This possible confounding was taken into account in the multivariate analyses summarized in Tables 3 and 4. The observed and adjusted values for each of the variables measured were not very different, indicating that, at most, only a small proportion of the observed relation can be explained by confounding.

The theophylline levels in a subgroup of the study population served as a measure of compliance; they provide evidence that the exposed and unexposed children followed medical advice similarly. These levels were obtained in a nonstandardized fashion as part of routine management, and in nearly all instances the children had been treated with theophylline for a considerable period of time.

Our findings are consistent with the results of studies of infants and children without asthma, in which more frequent respiratory infections and diminished pulmonary function were found to be associated with reported exposure to environmental tobacco smoke.[19-27] Dose–response relations have been identified between the degree of exposure to environmental tobacco smoke reported by parents and pulmonary function in one cohort of children with asthma[1,2] and in several studies of children without asthma.[22-24,27]

The urine cotinine levels in the current study indicate that parental reports are reliable when used to screen for exposure to environmental tobacco smoke in children with asthma. These observations provide further support for the results of published studies that rely on parental reports in examining the relation of exposure to environmental tobacco smoke and pulmonary morbidity. Urine cotinine levels can provide additional information when exposure to environmental tobacco smoke is reported, both in assessing the degree of actual intake (with its attendant risks) and in monitoring efforts to reduce exposure. The evidence that environmental tobacco smoke has a causal role in asthma-related morbidity is sufficiently strong, and the adverse pulmonary effects are sufficiently great, that systematic efforts to reduce inhalation of environmental tobacco smoke are warranted for children with asthma.

We are indebted to Josephine Williams, data-management analyst at the Foundation for Blood Research, for her assistance in coordinating the collection of data and patient samples; to the office

staff of Megathlin, Sigler, and Chilmonczyk for their assistance in patient enrollment, urine collection, and data retrieval; and to Robert Sigler, M.D., for referring some of the patients in the study.

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